REMARKS

1. Overview of Claim Amendments

Claim 1 has been amended to require

(1) that if a complex comprises more than one encoded molecule (we interpret the "an" of "an encoded molecule" as meaning "one or more), that all of the encoded molecules of that complex are identical (as otherwise the associate template would not be able to "identify" the encoded molecule),

(2) that the number of codons in the template equals the number of structural units in the encoded molecule complexed with that template,

(3) that each encoded molecule is a non-polymeric molecule with a core structure to which are attached a plurality of structural units.

Limitation (1) follows from the explicit requirement that the template "identify" the encoded molecule. If the "an" of "an encoded molecule" is interpreted to mean one or more, for the template to still identify the associated encoded molecule(s), then if there is more than one of them, they must be identical. (The preferred embodiment, in which the complex presents just one encoded molecule and one template, is the subject of new claim 45, with basis in, e.g., Figs. 1 and 2.

For basis for (2), see P7, L7-9.

Basis for (3) exists at P8, L11, wherein "polymers" and "scaffolds" are recited as alternatives. Thus, scaffolded molecules are non-polymeric.

A polymeric molecule **consists of** monomeric units, which may be the same or different, but if different will typically belong to a particular chemical class. The art considers polypeptides and polynucleotides to be polymeric molecules.

In polypeptides, the monomeric units are amino acids (strictly speaking, Pro is the closely related imino acid), and in polynucleotides, the monomeric units are nucleotides which in turn feature a nucleobase (a purine or pyrimidine) connected to a sugar (deoxyribose or ribose), the sugars themselves being

connected by phosphate groups.

Because claim 1 requires that the molecules be non-polymeric, it is no longer necessary to include specific exclusions of nucleic acids or of proteins composed of the twenty genetically encoded amino acids.

Page 6, lines 3-4 teaches, "The encoded molecule is formed by a variety of reactants which have reacted with each other and/or a scaffold molecule." (See also page 7, lines 12-13.) The role of the scaffold is further illuminated by page 6, lines 10-16:

> The formation of an encoded molecule generally starts by a scaffold, i.e. a chemical unit having one or more reactive groups capable of forming a connection to another reactive group positioned on a chemical entity, thereby generating an addition to the original scaffold. A second chemical entity may react with a reactive group also appearing on the original scaffold or a reactive group incorporated by the first chemical entity. Further chemical entities maybe involved in the formation of the final reaction product.

These reactants (chemical entities) are the precursors for the structural entities that appear in the final encoded molecule, see page 7, line 23-25. In like manner, the scaffold is the precursor for the core structure of the encoded molecule. See page 8, line 15.

Note that claim 1 now provides proper antecedent basis for "structural position" in claim 35.

Claim 2 has been amended to recite that "each encoded molecule is obtained by a process comprising the simultaneous or sequential reaction of each of two or more chemical entities with a reactive group of a scaffold having a plurality of reactive groups, wherein each chemical entity is a precursor for a structural unit appearing in the encoded molecule." The reaction of a chemical entity with a scaffold is disclosed on page 8.

It should be noted that the limitation of reacting a

plurality of chemical entities with a scaffold is not interpreted as excluding the possibility that a chemical entity may also be reacted with another chemical entity in the process of forming the encoded molecule. See P6, L10-15; P7, L12-13.

Claim 35 has been amended to require that the spacer sequence or sequences identify the structural position in the encoded molecule of one or more structural units identified by one or more codons within the template.

Claim 38 has been cancelled because it does not further limit claim 1 (cp. last clause of claim 1 as previously examined).

New claim 39 requires that each codon comprise at least six nucleotides and has basis at P22, L27-28, and cp. 3-20 at P4, L19-20 and 3-30 in claim 33.

New Claim 40 takes the limitation of claim 2 a step further, by requiring reaction of each of **at least three** chemical entities with a scaffold having **at least three** reactive groups. P8, L13-14 teaches, "One, two **or more** reactive groups intended for the formation of connections, are typically present on scaffolds." (Emphasis added). Note that in the synthesis of a linear oligopeptide or polypeptide, each amino acid has two reactive groups (NH2- and -COOH) intended for the formation of connections, so no linear oligopeptide or polypeptide can fairly be considered to comprise a scaffold to which three chemical entities were connected. Of course, such peptides were already excluded by the "non-polymeric" limitation.

New claim 41 requires that none of the structural units be one of the twenty genetically encoded amino acid residues. P1, L30-32 teaches that the structural units are not limited to the twenty genetically encoded amino acid residues, and the epitome of avoiding such limitation would be to exclude them entirely.

New claim 42 requires that none of them be amino acid residues, and is based on Fig. 4, which clearly contemplates reactions other than of amino and carboxy functions to form a peptide bond.

New claim 43 requires that the library collectively provides a number of chemically distinct codons which is equal to the number of chemically distinct structural units. In the Genetic Code, of course, the number of chemically distinct codons (64, although only 61 encode amino acids) is greater than the number of encoded amino acids (20); this is what is called "degeneracy".

The maximum diversity is possible if each chemically distinct codon encodes one and only one of the chemically distinct structural units, and this is clearly envisioned by P4, L13-18.

New claim 44 requires all of said encoded molecules comprise the same core structure, but the encoded molecules collectively exhibit variation in the choice of structural unit at each of a plurality of said structural positions. This is, of course, the simplest possible way of forming a library by reacting chemical entities with a scaffold.

New claim 45 requires that each complex is characterized by one and only one encoded molecule and one and only one template. The phraseology "an encoded molecule" encompasses just one, and likewise "a template" encompasses just one.

New claim 46 requires that the encoded molecules be small molecules with a molecular weight not greater than that of RGD. A preference for small molecules is expressed in example 1, and RGD is identified in that example as being a member of a small molecule library. This library is of course a polymeric molecule library but it is still useful for judging the meaning of small. R, G and D have molecular weights of 156.2, 57.06 and 115.09 daltons, respectively.

The library is identified as being a 27 member tripeptide library (P22, L14-18), and it is a combinatorial library with R, G or D occurring at each of the three positions (P22, L20-21). Hence, the largest member of the library is RRR, with a molecular weight of 468.6 daltons. This is reflected in claim 47.

New claim 48 is similar to amended claim 1 except that

instead of requiring that the encoded molecule be "non-polymeric", it requires that it not be a peptide or a nucleic acid. The requirement that it not be a nucleic acid was in claim 1 previously. The requirement that it not be a peptide is new and is based on PCT/DK02/000419 (published as WO 02/103008), which is incorporated by reference at P10, L23-25.
Since this application did not enter the US national phase, there is no domestically published application.

Referring first to page 115, lines 12-15, this teaches that "the enclosed invention, the template-displaying molecule technology, will for the first time allow direct selection of target-specific small non-peptide molecules independently of the translation process on the ribosome complex."

Then at page 164, lines 1-9, PCT '419 declares:

> Additional aspect of the present invention relates to i) a templated molecule comprising a sequence of covalently linked, functional groups, wherein the templated molecule does not comprise or consist of an α-peptide, or a nucleotide, ii) a templated molecule comprising a sequence of covalently linked, functional groups, wherein the templated molecule does not comprise or consist of a monosubstituted α-peptide or a nucleotide, and iii) a templated molecule comprising a sequence of covalently linked, functional groups, wherein the templated molecule does not comprise or consist of a peptide or a nucleotide.

In order to avoid objection that this is improper incorporation by reference of essential material, we have added a similar paragraph to our own specification. However, in the added paragraph we do not include the word "templated", because it is clear that while the present disclosure includes templated molecules (i.e., hybridization of building blocks comprising the chemical entities to a pre-formed template), see P12, L1-8), it is not limited to the templated technology (see P2, L10-19).

New claim 49 is dependent on 48 and requires that the library collectively provides at least about 10^3 different

encoded molecules. Basis is at PCT '419, page 164, lines 13-28, and page 18, line 30 to page 19, line 8, and the relevant paragraph, with the reference to "templated" excised, has been inserted into the present specification.

We note that besides supporting the "non-peptide" limitation of claim 48, PCT '419 also supports the term "non-polymeric" in claim 1. See page 159, lines 22-23. Some polymers which are not peptides or nucleic acids are identified within the tables on PCT '419 pp. 136-138.

2. Indefiniteness Issue

Claims 2-5, 12, 15, 16, 19, 25 and 37 stand rejected as indefinite because the examiner believes that it is unclear whether the invention is directed to a method or an apparatus. We traverse.

The examiner cites IPXL Holdings, LLC v. Amazon.com, Inc., 430 F.3d 1377 (Fed. Cir., November 21, 2005). The claim that the Federal Circuit held invalid read as follows

> 25. The system of claim 2 [including an input means] wherein the predicted transaction information comprises both a transaction type and transaction parameters associated with that transaction type, and the user uses the input means to either change the predicted transaction information or accept the displayed transaction type and transaction parameters. [emphasis by Court]

The Federal Circuit explained

> Thus, it is unclear whether infringement of claim 25 occurs when one creates a system that allows the user to change the predicted transaction information or accept the displayed transaction, or whether infringement occurs when the user actually uses the input means to change transaction information or uses the input means to accept a displayed transaction. Because claim 25 recites both a system and the method for using that system, it does not apprise a person of ordinary skill in the art of its scope, and it is invalid under section 112, paragraph 2.

The main claim here (1) is directed to a "microarray", which is a "manufacture", i.e., a product[1]. This microarray comprises immobilized probes, hybridized with a library of complexes, each complex comprising an encoded molecule and an identifying template.

Claim 2 recites that each encoded molecule is obtained by simultaneous or sequential reaction of two or more chemical entities. This is a process of making limitation. The reaction is further limited by claim 5. Claim 15 is dependent on 2 and limits how the probes are hybridized to the templates.

Claim 25 is similar to claim 2 except it refers to how the microarray is obtained, and refers to reaction of a nascent encoded molecule with a chemical entity to form the encoded molecule. Thus, it emphasizes the final step of the reaction contemplated by 2.

Claims 3, 4, 12, 16 ands 19 further limit the nature of the reaction contemplated by claim 25.

Thus, all of these claims are directed to products (microarrays) at least partially defined by the process of making them.

Claim 37 is a standard product-by-process claim, that is, it recites "wherein said microarray is obtained by a process comprising" various steps.

It is a well-established principle of American patent law that "a product-by-process claim, which is a product claim that defines the claimed product in terms of the product by which it is made, is proper". See MPEP 2173.05(p)(I). Likewise, product claims can include process-of-making limitations (i.e., without defining the complete process of manufacture).

In IPXL, the questioned limitations related to the method-of-use rather than to a process-of-making, and hence the decision did not hold that product claims with process-of-making limitations are improper.

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[1] The term "apparatus" does not actually appear in 35 USC 101.

Insofar as "use" limitations are concerned, there is a well-established distinction between claims to products that contains references to the manner "in which it is intended to be used", which is proper, and claims which actually claim both the product and its method of use. See MPEP 2173.05(p)(I). The claim 25 in the IPXL case might well have been acceptable if the claim had instead read, "said input means being capable of either changing the predicted transaction information or accepting the displayed transaction type and transaction parameters".

IPXL has been distinguished by the Federal Circuit in Microprocessor Enhancement Corp. v. Texas Instruments, Inc., Appeal No. 2007-1249, -1286 (Fed. Cir., April 1, 2008); http://www.cafc.uscourts.gov/opinions/07-1249.pdf .

The lower court in Microprocessor Enhancement had held that "although claim 1 purported to claim a method of executing instructions in a pipelined processor, the structural limitations of the pipelined processor evidence an intent to claim the apparatus as well." And it held that "although claim 7 purported to be an apparatus claim, the functional limitations are directed to the use of the apparatus rather than functional descriptions of certain claimed features of the apparatus." The Federal Circuit disagreed with both conclusions.

With regard to the method claim 1, the Federal Circuit began its analysis by noting that "Method claim preambles often recite the physical structures of a system in which the claimed method is practiced." It then pointed out that in IPXL, there was ambiguity as to whether infringement occurred when the system was created or when the user actually practiced the recited step. In contrast, in Microprocessor Enhancement, there was no ambiguity: "Direct infringement of claim 1 is clearly limited to practicing the claimed method in a pipelined processor possessing the requisite structure."

The court also upheld the apparatus claim. It began by noting that functional limitations in product claims do not

necessarily render the claim indefinite, citing K-2 Corp. v. Salomon S.A., 191 F.3d 1356, 1363 (Fed. Cir. 1999) ("analyzing functional language as an additional limitation to an apparatus claim for an in-line skate"). It also said that 35 USC 112 para. 6 can justify a functional limitation with insufficient structure, even when "means for" language is not explicitly used, citing Personalized Media Commc'ns, LLC v. Int'l Trade Comm'n, 161 F.3d 696, 703-04 (Fed. Cir. 1998). It went on to hold that "Claim 7 ... is clearly limited to a pipelined processor possessing the recited structure and capable of performing the recited functions, and is thus not indefinite under IPXL Holdings." (Emphasis in original).

3. Novelty Issue

The Examiner has rejected claims 1-5, 12, 15, 16, 19, 25-33, and 35-38 as allegedly anticipated by Winzeler as evidenced by Fegan et al.).

In the Examiner's opinion the Winzeler reference teaches the production of a microarray comprising immobilized single-stranded DNA probes hybridized to fluorescently labeled cDNA probes. According to the Examiner, the cyanine dyes (Cy3 and Cy5) constitute "encoded molecules" comprising a plurality of "structural units", while the cDNA constitutes a "template".

The Cy3-labeled fluorescent probes of Winzeler Fig. 1 were prepared by "enzymatic incorporation of Cy3-dCTP into cDNA by single round reverse transcription of poly(A)$^+$ mRNA from cultured Jurkat cells, essentially as described in Table III". Fig. 1 diagrams two different methods of linking Cy3 to the DNA (cytosine).

Footnote "d" to table III says, "to label mRNA with other fluors, substitute Fl12- or Cy5-dCTP in the reaction".

Both Cy3 and Cy5 could be present in a "two-color analysis" as described at the paragraph bridging Winzeler pages 9-10:

> Here target derived from mRNA from one condition is labeled with one fluor, whereas target from a different condition is labeled with a second fluor. Similar amounts of labeled material (usually cDNA) from the two samples are cohybridized to the microarray and the fluorescence intensity at the two appropriate emission wavelengths is determined. A good estimate of the relative differences in abundance of a target in the two samples can be obtained by comparing the ratio of the fluorescence intensities at the two wavelengths. By always using the same reference sample, microarrays produced using different sets of PCR products and by different individuals can be compared.

Claim 1 recites that each template comprises a "plurality of codons", that each encoded molecule comprises a plurality of structural units, and that "said encoded molecules collectively provide a plurality of chemically distinct structural units and said templates collectively provide a plurality of chemically distinct codons".

Page 6 of the action duplicates Fig. 1 from Fegan, showing attachment of a Cy3 dye to DNA by a common flexible linker (left) or a rigid ethynyl linker (right). The Cy3 dye proper is (ignoring the iodine substituent) compound 1 from Fegan Scheme 1, essentially two benzopyrroline ring systems linked by a three-carbon diene.

Fegan does not present the structure of Cy5. According to Wikipedia/Cyanine, Cy5 differs from Cy3 in that the two rings are connected by a five-atom triene rather than a three-atom diene.

According to the Examiner, "with regard to figure 1 above, the 'template is the DNA (sugar and base) and the 'structural units' can be anyone of the 5 or 6 membered rings as well as carbon linkages between such rings. Thus, given that the 'encoding' function of the probe and template molecules is an intended use, one can think of the individual

nucleotide bases of A, T, C, G, or virtually any combination of the bases (e.g. a base triplet) of the genes (see Kahn, fig. 10, for example) as coding for a structural unit of the fluorescent molecule".

However, the Winzeler disclosure cannot be so read on the subject matter of claim 1 because of the further limitations of claim 1:

(1) "each codon in a given template identifying a structure unit in the encoded molecule with which it is complexed".

(2) "wherein each chemically distinct codon identifies one and only one chemically distinct structural unit".

The examiner errs by characterizing the "encoding function" as a mere statement of "intended use". It in fact limits what combinations of codons and structural units may occur in the complexes of a given library. To make this clear, let us begin by contemplating a simple system, in which the templates are all two bases long. For the templates to comprise a plurality of codons, each codon must perforce be a single base, and each template is then two codons. For <u>each codon</u> of a given template to identify that a particular structural unit is present in the associated encoded molecule, there must then be an equal number of encoded structural units per encoded molecule... in this example, two[2]. If we use the standard DNA bases (A, C, G, T), then we have 4^2=16 different templates and thus 16 different encoded molecules.

If we are choosing our codons from the four possibilities A, C, G and T, then can be no more than four possible structural units, which we will call W, X, Y and Z.

If so, then the library could not contain the complex AA-WX, because A could encode W or X, but not both.

The library could contain the complex AA-WW, but if it

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[2] There could also be a moiety that is unencoded, e.g., a "scaffold" or a "linker".

did, it could not also contain the complex AA-XX, because then again A would be encoding both W and X.

Claim 1 only requires that the template identify chemical entities were reacted in the course of making the encoded molecule, not where they were reacted. Claim 27 requires a general correlation between the position of the codon in the template and the position of the corresponding structural unit in the encoded molecule. Thus, if the library of claim 27 contained the complex AC-WX, it could not also contain AC-XW.

When the number of different codons, structural units, encoded molecules and templates in a library are large, the structural constraints become more complex, but they are no less real because they are more tedious to set forth than in our simple 2 codons/1 base per codon/ 4 possible bases example. The limitations are structural limitations, not mere statements of intended use.

Keeping this in mind, we return to consideration of Winzeler and ask, is there any possible "designation" of codons and corresponding structural units that is consistent both with Winzeler's disclosures and our claim 1? We think not.

Bear in mind that Winzeler only labels cytosine. In the Cy3 sublibrary from DNA sample #1, every DNA molecule is labeled at every cytosine with Cy3. In the Cy5 sublibrary from DNA sample #2, every DNA molecule is labeled at every cytosine with Cy5.

Clearly, there will be DNA molecules which appear in both samples, and thus in the cohybridized library the same DNA sequence will be associated in come complexes with Cy3 and in others with Cy5. But the same DNA sequence cannot "identify" both Cy3 and Cy5, because the latter differ from each other. So whether you consider the "codon" in Winzeler to be a single base or a combination of bases, Winzeler's "two color" library will violate limitation (2) above, because whatever codon is said to identify the linkage between the two ring systems is

identifying both the three carbon diene of Cy3 and the five carbon triene of Cy5.

Moreover, we must question whether in Winzeler, the A, G or T can be said to be codons or even parts of codons. Winzeler only labeled the cytosines; if a particular DNA were cytosine-free, it would contain neither Cy3 nor Cy5. And if it contained cytosines, they would be labeled with Cy3 or Cy5 without regard to the nature of the flanking bases.

We respectfully suggest that since Winzeler only labeled cytosines, his codons were only those cytosines, and the A, G and Ts were merely spacers between codons.

While claim 1 does not exclude the possibility of a one-base codon[3], it does require that complexes collectively provide a plurality of chemically distinct codons, Winzeler only provides one codon -- cytosine (C) -- to "encode" both Cy3 and Cy5, and thus violates another limitation of claim 1.

For Winzeler's system to anticipate claim 1, the following must be true

(A) all of the DNAs attached to Cy3 must have the same subsequence(s) in common with the DNAs attached to Cy5 to represent the structural unit(s) which are identical in Cy3 and Cy5;

(B) all of the DNAs attached to Cy3 must have one or more subsequences which differ from the aligned subsequences of the DNAs attached to Cy5, to represent the structural units which differ between Cy3 and Cy5.

These conditions, which follow from the "identifying" limitation, are not met.

In drafting the quoted language of claim 1, we had in mind the relationship of DNA to protein. Each DNA sequence can code for (identify) one and only one protein sequence. However, because of the structure of the Genetic Code (1-6 different codons can identify a given amino acid), a given protein sequence is typically encoded by many different DNA

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[3] Which is excluded by old claim 33 and new claim 39.

sequences.

Claim 29 further distinguishes Winzeler in that it reverses limitation (2) above, i.e., requires that each chemically distinct structural unit be identified by one and only one of the chemically distinct codons. Clearly, any interpretation of Winzeler would have both Cy3 and Cy5 identified by cytosine. Even if the codon were interpreted to include flanking bases, it would be expected that if say ACT appeared in the Cy3 library it would also appear in the Cy5 library.

The Examiner regards the terms "spacer sequence" and "priming sites" of claims 35 and 36 as mere intended uses of the claimed sequences taught by Winzeler. We do not agree with this assessment.

A spacer sequence is a sequence separating one codon from another. P4,, L25-28. Now, we agree that if we characterize Winzeler's cytosine as her codons, then the intervening A's, G's and T's are spacer sequences. But claim 35 does not merely require that there be a spacer, but that the combination of codon and spacer identify the structural position of one or more codons within said template. By this we mean that a probe that hybridizes to a target sequence comprising a particular codon and a particular position-identifying spacer sequence will not hybridize to the combination of same codon and any other position-identifying spacer sequence under the same hybridization conditions.

4. Obviousness Issue

Claims 1 to 5, 12, 16, 19 and 25 to 38 are rejected as being obvious over Szostak in view of Schultz. Additionally, claims 7, 15, 18 and 21 are rejected as obvious over the above references in view of Felder

Szostak teaches microchips comprising RNA-protein fusions and Schultz teaches methods for in vitro incorporation of un-natural amino acids to produce novel un-natural proteins.

In Szostak's library, the RNA is fused to encoded molecules that are **polymeric** in nature, composed solely of amino acid residues. Schultz at most motivates the art to replace one or more of the twenty genetically encodes amino acids in Szostak's proteins with an un-natural amino acid. However, the result would still be fusions of RNA to polymeric molecules.

Since amended claim 1 requires that the encoded molecule be non-polymeric, it clearly is directed to subject matter that is not disclosed or suggested by the combination of Szostak and Schultz.

Felder is cited merely to show the possibility of immobilizing a target-binding "linker" oligo to a support by means of its hybridization to an immobilized anchor oligo. It does not overcome the deficiencies of Szostak and Schultz vis-a-vis amended claim 1.

New claim 48 alternatively distinguishes Szostak and Schultz by requiring that the encoded molecules not be peptides. Even if an unnatural amino acid per Schultz is incorporated into Szostak's proteins, they remain peptides.

Respectfully submitted,

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